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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/080,127	05/15/98	BLINKOVSKY A	5253.200-US

HM12/0523

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EXAMINER	
TURNER, S	
ART UNIT	**PAPER NUMBER**
1644	13

DATE MAILED: 05/23/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/080,127	Applicant(s) Blinkovsky
	Examiner Sharon L. Turner, Ph.D.	Group Art Unit 1644

☒ Responsive to communication(s) filed on *2-29-00*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *90-129* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *90-129* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

1. The Examiner of U.S. Patent application SN 09/080,127 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Examiner Turner, Technology Center 1600, Art Unit 1644.

2. The amendment filed 2-29-00 has been entered into the record and has been fully considered. Claims 46-89 are canceled. Claims 90-129 are pending.

3. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner in view of the new rejections set forth below.

New Rejections

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 90-129 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses SEQ ID NO's: 1 and 2 which correspond respectively to the nucleotide sequence and the amino acid sequence of an *Aspergillus* aminopeptidase. These SEQ

ID NO's meet the written description provisions of 35 USC 112, first paragraph. However, the claims are directed to or encompass corresponding polypeptides from other species, mutated peptides, peptides produced from allelic variants, splice variants, peptide sequences that have a recited degree of identity (similarity, homology), peptides having physicochemical properties of: a pH optimum in the range of from about pH 7.27 to about pH 10.95 determined at ambient temperature in the presence of Ala-para-nitroanilide, a temperature stability of 90% or more relative to initial activity at pH 7.5 determined after incubation for 20 minutes at 60°C in the absence of substrate and an ability to hydrolyze a substrate containing Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Phe, Pro, Ser, Thr, Trp, Tyr, or Val at its N-terminus wherein the polypeptide having aminopeptidase activity sequentially removes one amino acid residue at a time fro the N-terminus of a peptide, polypeptide or protein; and a peptide which is encoded by a nucleic acid sequence which hybridizes. None of these sequences meets the written description provision of 35 USC 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO's:1 and 2 of the instant application, the skilled artisan cannot envision the detailed chemical structure of the encompassed amino acids and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity

or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific nucleic and amino acids are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO's:1 and 2 , but not the full breadth of claims meet the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

5. Claims 90-129 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the aminopeptidase of residues 16-496 of SEQ ID NO:2, does not reasonably provide enablement for polypeptides of claims 90-129. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation.

As to claims 90-129 with respect to % identity, allelic variants and fragments which retain aminopeptidase activity, Choh et al., PNAS 77(6):3211-3214, June 1980, clearly teach that even highly related polypeptides with different amino acid sequences exhibit distinct biological activities and divergent immunoreactivity. The specification does not teach any peptide which corresponds to the recited % identity or fragment thereof, which retains aminopeptidase activity or possesses the physicochemical properties of; a pH optimum in the range of from about pH 7.27 to about pH 10.95 determined at ambient temperature in the presence of Ala-para-nitroanilide, a temperature stability of 90% or more relative to initial activity at pH 7.5 determined after incubation for 20 minutes at 60°C in the absence of substrate and an ability to hydrolyze a substrate containing Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Phe, Pro, Ser, Thr, Trp, Tyr, or Val at its N-terminus wherein the polypeptide having aminopeptidase activity sequentially removes one amino acid residue at a time fro the N-terminus of a peptide, polypeptide or protein.

As to claims 90-129 with respect to hybridizing nucleotides, the skilled artisan recognizes that hybridizing nucleic acids are dependent upon the specific residues, the G+C content, the hybridization conditions and the length of the hybridizing sequences, see in particular Jenkins et al., PCR Methods and Applications S77-82, 1994. The specification fails to teach any hybridizing nucleic acids which encode a peptide having the recited identity, a fragment thereof, a peptide which retains aminopeptidase activity or the physicochemical properties of; a pH optimum in the range of from about pH 7.27 to about pH 10.95 determined at ambient

temperature in the presence of Ala-para-nitroanilide, a temperature stability of 90% or more relative to initial activity at pH 7.5 determined after incubation for 20 minutes at 60°C in the absence of substrate and an ability to hydrolyze a substrate containing Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Phe, Pro, Ser, Thr, Trp, Tyr, or Val at its N-terminus wherein the polypeptide having aminopeptidase activity sequentially removes one amino acid residue at a time fro the N-terminus of a peptide, polypeptide or protein.

As to claims 90-129 with respect to hybridizing and complementary strands, the skilled artisan is well aware that the complementary nucleotides and sequences which hybridize to the coding strand, i.e., the non-coding strand, are unrelated to the coding sequence. Thus, applicant is not enabled for the use of a vector and host cell expressing the complementary strand or hybridizing sequences which encodes a aminopeptidase because the protein encoded by the opposite strand is unrelated both structurally and functionally to aminopeptidase sequences.

Thus, in view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue experimentation for the skilled artisan to make and use the claimed invention.

With respect to applicants traversal of the previous enablement rejection and as it is pertinent to the new rejection of record over claims 90-129, applicants argue that the specification provides instructions on how to obtain the polypeptides, in particular p. 4, line 9 to p. 6, line 17, that hybridization conditions and protocols are provided on p. 5, line 18 to p. 6, line

18, and that one of skill in the art would know how to identify and isolate such analogs given the teachings disclosed in the specification.

Applicant's arguments filed 2-29-00 have been fully considered but they are not persuasive. The specifications guidance does not enable a skilled artisan to obtain the appropriate peptides. For example, the specification does not provide a specific probe, hybridization conditions or a library from which an aminopeptidase with the claimed characteristics may be isolated. The artisan, based on the limited guidance is not reasonably assured of reproducibly and reliably obtaining the claimed aminopeptidases as directed. Further, the artisan would be forced, after obtaining a candidate agent to perform undue experimentation to determine the full open reading frame, express the protein and determine the peptides biological properties as well as its functional characteristics. The specification is required to be fully enabled at the time of the invention. However, applicants do not provide evidence of reduction to practice for any other aminopeptidase other that of SEQ ID NO:2. The specification merely invites the artisan to discover other related sequences. The single species does not support the genus claim. For these reasons, applicants arguments are not persuasive.

6. Claims 110 and 129 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of plasmid pEJG18 in *E. coli* NRRL B-21677. Because it is not clear that cell lines possessing the properties of plasmid pEJG18 in *E. coli* NRRL B-21677 are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the claims require the use of plasmid pEJG18 in *E. coli* NRRL B-21677, a suitable deposit for patent purposes is required. Accordingly, filing of evidence of the reproducible production of the cell line claimed in claims 110 and 129, is required. Without publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the cell line is an unpredictable event.

Applicant's referral to plasmid pEJG18 in *E. coli* NRRL B-21677 is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR § 1.801-1.809 have been met.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of the patent on this application. These requirements are necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR § 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a

statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;
2) The name and address of the depositor;
3) The date of deposit;
4) The identity of the deposit and the accession number given by the depository;
5) The date of the viability test;
6) The procedures used to obtain a sample if the test is not done by the depository; and
7) A statement that the deposit is capable of reproduction.

As a means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the plasmid pEJG18 in *E. coli* NRRL B-21677 cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR § 1.801-1.809 for further information concerning deposit practice.

7. Claims 90-129 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 90-129 recite the new limitation, "wherein the polypeptide having aminopeptidase activity sequentially removes one amino acid residue at a time from the N-terminus of a peptide, polypeptide, or protein." Applicants do not refer to the specification where support may be found. The examiner notes that the specification defines p. 3, line 38 to p. 4, line 2 the term "aminopeptidase activity" as a peptidase which catalyzes the removal of amino acids from the N-terminal end of peptides, oligopeptides or proteins. It appears that the specification does not limit the removal to single amino acids as the use of removal within this definition is plural with respect to amino acids. Thus, the recitation "wherein the polypeptide having aminopeptidase activity sequentially removes one amino acid residue at a time from the N-terminus of a peptide, polypeptide, or protein" constitutes new matter.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 90-129 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 90-129 recite medium stringency conditions. The artisan can not determine the metes and bounds of the hybridizing nucleic acids because the definition of medium stringency conditions is not specified. The skilled artisan recognizes that hybridization is dependent upon the specific residues, the G+C content, the hybridization conditions (salt concentration, temperature) and the length of the hybridizing sequences, see in particular Jenkins et al., PCR Methods and Applications S77-82, 1994. Thus, for these reasons the claims are indefinite with respect to the amino acids encompassed.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 90-129 are rejected under 35 U.S.C. 102(b) as being anticipated by Kauppinen et al., WO96/28542, September 19, 1996.

Kauppinen et al., disclose an *Aspergillus oryzae* aminopeptidase which cleaves peptides. The proteins of instant claims share a single amino acid fragment with the WO96/28542

aminopeptidase. The reference is silent as to the sequential cleavage of single amino acids from the N-terminus of proteins, however as argued by applicants with respect to Taylor, 1993, The FASEB J., 7:290-298, which defines an aminopeptidase at p. 290, column 2, first complete paragraph, the term aminopeptidase refers to removal of a single amino acid at the N-terminus. The biochemical properties and functional activity are inherent to the aminopeptidase taught by Kauppinen. Thus, Kauppinen anticipates the claimed invention.

12. Claims 90-129 are rejected under 35 U.S.C. 102(b) as being anticipated by Nishizawa et al., J. Biol. Chem., 269:13651-55, 1994.

Nishizawa teach a *S. cerevisiae* aminopeptidase which hybridizes with SEQ ID NO:1, its complementary strand and a subsequence of SEQ ID NO:1 which retains aminopeptidase activity, is a fragment of a, b or c which retains aminopeptidase activity and which inherently has the physicochemical properties of e, see in particular attached alignment of amino acids. As set forth above with respect to Taylor, 1993, FASEB J., 7:290-298, which defines an aminopeptidase at p. 290, column 2, first complete paragraph, the term aminopeptidase refers to removal of a single amino acid at the N-terminus. Thus, Nishizawa anticipates the claimed invention.

Status of Claims

13. No claims are allowed.

Conclusion

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973.

Sharon L. Turner, Ph.D.
May 22, 2000

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640